Invited Review

Collagen types VIII and X, two non-fibrillar, short-chain collagens. Structure homologies, functions and involvement in pathology

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Summary. Collagens can be divided into two groups, i.e., fibrillar and non-fibrillar collagens. Short-chain collagens, a subgroup of non-fibrillar collagens, comprises collagen type VIII and type X. These two collagen types show several similarities in structure and possibly also in function. Type VIII collagen appears to be secreted by rapidly proliferating cells. It can be found in basement membranes and may serve as a molecular bridge between different types of matrix molecules. In different tissues this collagen type may serve different functions. Stabilization of membranes, angiogenesis, and interactions with other extracellular matrix molecules. Since collagen type X is produced by hypertrophic chondrocytes, this collagen type can only be found in matrix of the hypertrophic zone of the epiphyseal growth plate cartilage. Collagen type X is probably involved in the process of mineralization, endochondral ossification, and is also proposed to play a role in angiogenesis. Collagen types VII and X may be involved in matrix and bone disorders. Their structure, function, and involvement in pathology are discussed in this review.

Key words: Short-chain collagens, Collagen type VIII, Collagen type X

Introduction

Collagens are extracellular, structural proteins present in all multicellular species. They originally have been assigned a structural role in the extracellular matrix (ECM) (Borstein and Sage, 1980). Collagens are synthesized as pro-collagens in which the triple helical domain is flanked by C- and N-terminal globular extensions (Brass et al., 1992). Nineteen collagen types have been described so far (van der Rest and Garrone, 1991; Kielty et al., 1993; Mayne and Brewton, 1993;

Prockop and Kivirikko, 1995). At least 30 genes are involved to code for the constituent polypeptide chains of all these homo- or hetero-trimeric molecules (Rehn et al., 1994). Collagens can be divided into two groups, i.e., fibrillar and non-fibrillar collagens, and the latter into several subgroups (Kivirikko et al., 1995). Table 1 presents an overview of the structures formed by collagens, their constituent chains, and their localization.

Fibrillar collagens

The major function of fibrillar collagens is supportive and mechanical (Bornstein and Sage, 1980). They are important for embryonic morphogenetic events as well (Ninomiya et al., 1986). The subfamily of collagens forming quarter-staggered fibrils (I, II, III, V, XI) is best known (van der Rest et al., 1993). They contain a continuous triple helical domain formed by α chains with molecular weights exceeding 95 kD (Dublet et al., 1989).

The fibrillar collagen genes are closely related and clearly derived from a single ancestral gene. The intron-exon structure of all vertebrate fibrillar collagen genes is essentially identical for the region of the gene encoding the large triple helix. The greatest differences between the various fibrillar collagen chains are noted in the N-propeptide region (van der Rest et al., 1993). Their COOH-terminal propeptides are highly homologous between themselves, and their modes of aggregation appear to be very similar as well (van der Rest et al., 1993).

Non-fibrillar collagens

The collagen types IV, VI, VII, and XII also contain α chains with molecular weights of over 95 kD, but their triple helical domains are interrupted by nonhelical segments (Dublet et al., 1989). Non-fibrillar collagen types consist of three identical α chains while other types consist of two or more genetically distinct but similar polypeptides (Burgeson, 1988; Dublet et al.,

Table 1. Structures formed by collagens, and their locations.

COLLAGEN TYPE	STRUCTURES FORMED	TYPE NUMBER	CONSTITUENT CHAIN	DESCRIBED IN
Fibrillar	Quarter staggered fibrils	Type I[1]	α1(I)	Dentin, skin
			α2(I)	Most connective tissues
		Tipe II[1, 2]	α1(II)	Hyaline cartilage
		Type III[1]	α1(III)	Fertal skin, vessel walls, soft connective tissues
		Type V[1, 2, 3, 4]	α1(V)	Chinese hamster lung cells
			α2(V)	Most type I collagen containing tissue
			α3(V)	Placenta
		Tuype XI[1,2,3,4]	α1(XI)	Cartilages
			α2(XI)	Bovine bone, endothelial cells
			α3(XI)	
	Basement membranes	Type IV[5]	α1(IV)	Basement membranes
			α2(IV)	
			α3(IV)	Glomerular basement membranes
			α3(IV)	
			α4(IV)	
			α5(IV)	
			α6(IV)	
Non-fibrillar	Hexagonal lattices (short-chain)	Type VIII[6, 22]	α1(VIII)	Descemet's membrane, endothelial cells
			α2(VIII)	
		Type X[7, 8, 22]	α1(X)	Growth plate cartilage
	Beaded filaments	Type VI[9, 10]	α1(VI)	Most connective tissues
			α2(VI)	
			α3(VI)	
	Fibril associated (FACIT)	Type IX[11-13, 22]	α1(IX)	Cartilage
			α2(IX)	
			α3(IX)	
		Type XII[13, 14, 22]	α1(XII)	Tendon, skin
		Type XIV[14, 22]	α1(XIV)	Skin, tendon
		Type XVI[19, 22]	α1(XVI)	
		Type XIX[20]	α1(XIX)	
	Anchoring fibrils	Type VII[15]	α1(VII)	Mesenchyme-epithelial junctions
	Multiplexins	Type XV[21-24]	α1(XV)	
		Type XVIII[21-23 ,25]	α1(XVIII)	
	Others	Type XIII[16-18, 22]	α1(XIII)	Epithelial and endothelial cells
		Type XVII[22]	α1(XVII)	

[1]: Dion and Myers, 1987; [2]: Morris and Bächinger, 1987; [3]: Niyibizi and Eyre, 1989; [4]: Brown et al., 1991; [5]: Hostikka et al., 1990; [6]: Sawada et al., 1990; [7]: Yamaguchi et al., 1989; [8]: Muragaki et al., 1991a; [9]: Bonaldo and Colombotti, 1989; [10]: Chu et al., 1990; [11]: Wu and Eyre, 1989; [12]: Eyre et al., 1987; [13]: Shaw and Olsen, 1991; [14]: Aubert-Foucher et al., 1992, [15]: Keene et al., 1987; [16]: Pihlajaniemi and Tamminen, 1990; [17]: Tikka et al., 1991; [18]: Juvonen et al., 1992; [19]: Yamaguchi et al., 1992; [20]: Inoguchi et al., 1995; [21]: Rehn et al., 1994; [22]: Fukai et al., 1994; [23]: Oh et al., 1994; [24]: Kivirikko et al., 1995; [25]: Tajima and Tokimitsu, 1995.

1989). Non-fibrillar collagen types are distinctly different from fibrillar collagen types, in that they are unable to form fibrils. Several subfamilies can be distinguished among non-fibrillar collagens, based on comparisons of the protein structures and of the intron-exon gene organizations (van der Rest et al., 1993; Fukai et al., 1994; Inoguchi et al., 1995). Type IV collagen is a separate subgroup present in basement membranes. Another subgroup comprises the short-chain collagens to which the collagen types VIII and X belong (Yamaguchi et al., 1989; Sawada et al., 1990; Muragaki et al.,

1991a). Type VI collagen, not assigned to a certain subgroup, forms beaded filaments (Bonaldo and Colombatti, 1989; Chu et al., 1990). The abbreviation FACIT (Fibril Associated Collagens with Interrupted Triple-helices) has been proposed for the subfamily comprising types IX, XII, XIV, XVI, and XIX collagens. These collagens are closely associated with the fibrillar collagens and are characterized by the presence of a short triple helical domain located near the carboxyl end of the molecule (van der Rest et al., 1993; Fukai et al., 1994). Another subgroup, the multiplexins, comprise

collagen types XV and XVIII. The non-fibrillar collagen types XIII and XVII have not been assigned to a certain subgroup (Fukai et al., 1994).

Short chain collagens

The short-chain collagens, i.e., types VIII and X, are composed of α chains with molecular weights less then 95 kD (Olsen et al., 1985; Yamaguchi et al., 1989). Despite similarities in domain structure, amino acid sequences, and genomic exon configurations, short-chain collagen and fibrillar collagens show very different temporal and spatial expression (Olsen and Ninomiya, 1993).

Initially collagen types VI and X were referred to as short-chain collagens. When additional collagens in the smaller size range were discovered (Sage et al., 1983a; van der Rest et al., 1985) it was suggested that the term short-chain collagen should be used to designate the whole group of collagens whose unprocessed biosynthetic molecules contain polypeptides shorter than type I collagen α chains (Olsen et al., 1985). The two members within the group of short-chain collagens can be identified either by a descriptive name based on the specific tissue distribution of the collagen or by designation of their type (Olsen et al., 1985).

Collagen type VIII

Structure

Type VIII collagen was first called endothelial cell (EC) collagen. It possesses several characteristics distinct from those of other collagen species such as lack of interchain disulfide cross-links, and extreme sensitivity to pepsin digestion. Chains of three different molecular masses (177 kD (EC1), 125 kD (EC2), and 100 kD (EC3)) have been identified (Sawada et al., 1990). Type VIII collagen is probably a heterotrimer, but the existence of homotrimeric molecules composed entirely of α1(VIII) or α2(VIII) chains cannot be ruled out (Muragaki et al., 1991a; Rosenblum, 1995).

On the basis of careful biochemical analysis, Benya and Padilla (1986) postulated that the native chain of type VIII collagen is 61 kD and that 120- and 170-kD components are ß- and γ-components of the collagen molecule. They presented an alternative model in which the type VIII collagen molecule is composed of a homotrimer of 641-kD chains with non-triple-helical domains at both ends (Benya and Padilla, 1986). Yamaguchi et al. (1989) have suggested that strong non-covalent, acid-labile interactions and covalent cross-links between the subunits might produce the oligomers of 120 and 180 kD. Kapoor et al. (1986) presented evidence that the 61-kD chain does not have immunological cross-reactivity to EC2.

An interrupted helix model for type VIII collagen proposed by Benya (1980) showed the molecule as a homotrimer which subunits of Mr 180,000 Da

containing interruptions in the Gly-X-Y repeat structure at sites located one-third and two-thirds of the length of the molecule. Subsequently, Sage et al. (1983b) proposed a similar «cassette» model based on additional evidence from the study of the molecule synthesized by bovine aortic endothelial cell cultures (Yamaguchi et al., 1989).

Characterization of type VIII collagen chains took place by cloning and sequencing of cDNAs, since there are only small amounts of this collagen present in tissues (Yamaguchi et al., 1989). Chromosomal locations for the human α1(VIII) and α2(VIII) genes have been mapped on chromosomes 3 and 1, respectively (Fig. 1) (Muragaki et al., 1991a,b).

Yamaguchi et al. (1989) have isolated two overlapping cDNA clones covering 2425 base pairs encoding a short type VIII collagen chain synthesized by rabbit corneal endothelial cells. The CDNA clones encode an open reading frame of 744 amino acid residues containing a triple-helical domain of 454 residues flanked by 117 and 173 residue amino and carboxyl non-triple-helical domains (called NC2 and NC1, respectively (Sawada, 1982; Sawada et al., 1984).

Analysis of the amino acid sequence of the amino terminal NC2 domain shows that it is cationic in nature with a calculated pI of 10.55 while the pI of the NC1 domain in 8.68. Vasios et al. (1988) speculated that a polyanionic glycosaminoglycan such as heparan sulphate could electrostatically interact with type VIII collagen, particularly at the NC2 domain as proposed between the amino terminal NC4 domain (calculated pI 9.4) of the α1(IX) chain and cartilage matrix molecules with polyanionic moieties.
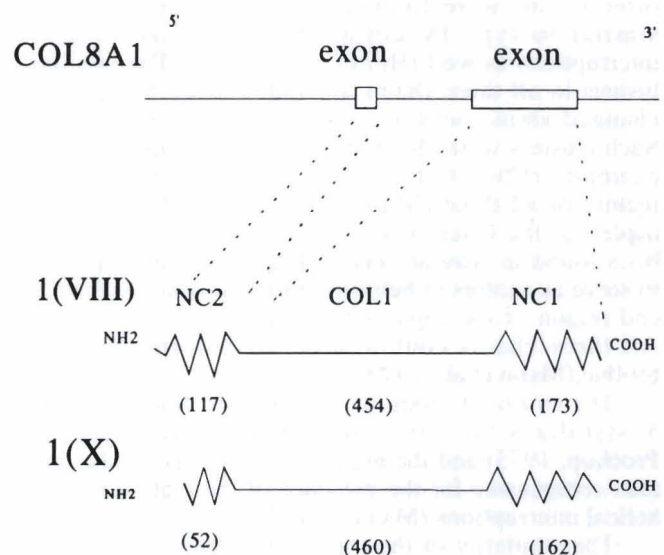
The cDNA-derived sequence of the COL1 domain

Fig. 1. Diagram showing the partial exon-structure of the human genomic DNA encoding for the α1(VIII) collagen chain, its translation product, and the translation product of the α1(X) collagen chain

of α1(VIII) contains 80 prolyl residues in the Y-positions of Gly-X-Y triplets, which are likely to be sites of hydroxylation. This potentially high hydroxy-proline content may result in a high thermal stability of the triple-helix. The high hydroxyproline content of α1(VIII) is similar to that of α1(X) collagen chains (Yamaguchi et al., 1989).

The starting material for the investigation of the primary structure of a triple-helical domain of collagen type VIII was the triple-helical domain described by Kapoor et al. (1986) and Jander et al. (1990) as the major product from pepsin cleavage of type VIII collagen. After denaturation two chains were separated by HPLC and identified by their N-terminal sequences as the α2(VIII) and α1(VIII) (Mann et al., 1990). The α2(VIII) fragment contains a triple-helical stretch of 460 amino acid residues flanked by short non-triple helical remnants of the N- and C-terminal globular domains which were destroyed during pepsin extraction of Descemet's membrane (Mann et al., 1990).

The triple-helical sequence is interrupted by 8 somatic point mutations. Two of them were of the type Gly-X-Y-X-Y-Gly and six of the type Gly-X-Gly. These imperfections were probably generated by deletion of a glycyl residue and by deletion of a residue in X or Y position, respectively (Mann et al., 1990).

The fact that 8 triple-helical imperfections are conserved in all three α-chains shows the importance of this structural feature which introduces flexibility to the rigid triple-helix. As far as the point mutations are concerned, the α2(VIII) chain is more similar to α1(X) than to α1(VIII), since two of the three point mutations of the larger type Gly-X-Y-X-Y-Gly found in type X (Martin et al., 1985) were matched by similar point mutations in α2(VIII). Most of the point mutations in all three chains were followed by a lysyl residue. This similar to type IV collagen, which has frequent interruptions as well (Brazel et al., 1988). The modified lysines in all three chains are followed by a negatively changed amino acid in position X of the next triplet. Such clusters were also found in other collagens (VI for example) (Chu et al., 1988). Another well-preserved feature of all three chains is the block of Gly-Pro-Hyp triplets at the C-terminal end. Similar blocks have also been found in several other collagens and are supposed to serve as centres in helix formation and to stabilize the end region of the triple helix (Sakakibara et al., 1973). All three chains contain more hydroxyproline than proline (Mann et al., 1990).

The hydroxyl group of 4-hydroxyproline in position Y stabilizes the triple-helical structure (Berg and Prockop, 1973) and the high content of this residue may thus compensate for the presence of the eight non-triple helical interruptions (Mann et al., 1990).

The similarity of the triple-helical areas of α1(VIII) and α2(VIII) in length, location and number of point mutations suggests that both chains together from the 120-140 nm long triple helical domain of the molecule (Jander et al., 1990).

Mann et al. (1990) observed a ratio of α1(VIII)/α2(VIII) between 1.5 and 2. Since no other chain type was found a chain composition of [α1(VIII)2α2(VIII)] for the type VIII collagen molecule has been proposed. Rosenblum (1995) recently described a homotrimeric assembly of α1(VIII) collagen chains. The molecular mass and molecular model of type VIII collagen are currently under debate, and further study of the interactions of α1(VIII) collagen chains with another, and with α2(VIII) chains and other matrix components is needed (Rosenblum, 1995).

Before discussing the function of collagen type VIII, the cellular source of this collagen type and its tissue distribution should be reviewed.

Cellular source

Type VIII collagen was originally identified in the cell culture medium of bovine aortic endothelial cells (Sage et al., 1980), corneal endothelial cells (Benya, 1980), and several tumor cell lines (Alitalo et al., 1983; Sage et al., 1984). Not all endothelial cells synthesize type VIII collagen and the protein is not restricted to the vascular endothelium (Alitalo et al., 1983; Sage et al., 1984). There was no detection of collagen type VIII with immunofluorescence in highly vascularized tissues like lung and liver. Type VIII collagen was preferentially recovered from the culture medium of rapidly proliferating and migrating cells *in vitro*. It might therefore only be expressed during the development of the vasculature or in adults as a result of vascular injury (Yamaguchi et al., 1989). Rapidly proliferating cells appear to secrete high levels of type VIII collagen in the medium, while no type VIII collagen is recovered from the medium of quiescent, confluent cells (Alitalo et al., 1983; Sage et al., 1986). Some platelet components, including platelet-derived growth factor seem to inhibit the production of type VIII collagen by bovine aortic endothelial ells (Yamaguchi et al., 1989). Study of the cornea has resulted in the discovery of matrix components which are structurally distinct from fibrillar and basement membrane type collagens. These matrix components play a unique role in matrix organization (Rosenblum et al., 1993).

Descemet's membrane (DM) is the basement membrane of corneal endothelial cells, which has an extremely thick basal lamina (Kefalides et al., 1976). DMs of some animal species contain characteristic stacks of hexagonal lattices that are arranged parallel to the surface of the membrane (Alitalo et al., 1983). The lattice has been regarded as collagenous (Sawada, 1982; Alitalo et al., 1983), and type VIII collagen (Kapoor et al., 1988) has been postulated as a candidate component (Sawada et al., 1990).

It is possible that type VIII collagen is a product of undifferentiated or stem cells and that the type VIII gene is reactivated during cellular proliferation as a result of injury (Kapoor et al., 1988). Actively proliferating cultured astrocytoma cells show a heightened production

of type VIII collagen as well (Alitalo et al., 1983). Rosenblum et al. (1990, 1993) showed that rat mesangial cells produce type VIII collagen, and Rüger et al. (1994) showed *in vivo* production of type VIII collagen by human mast cells.

The development of extracellular matrix may be influenced by mast cells since they are able to elaborate proteases and cytokines. Human mast cells are also associated with fibrosing conditions. The primary contribution of mast cells to extracellular matrix construction might be the production of as collagen type VIII scaffold, since human mast cells produce no collagen types, other than collagen type VIII *in vivo* (Rüger et al., 1994).

Tissue distribution

Type VIII collagen is synthesized by only a few cell types, but can be distributed in various tissues. A pepsin-resistant triple helical domain of type VIII collagen was isolated from bovine corneal DM and used as an immunogen for the production of monoclonal antibodies (mAbs) (Alitalo et al., 1983). Immunofluorescence studies with these mAbs showed that type VIII collagen was deposited as fibrils in the extracellular matrix of corneal endothelial cells, and also in various other tissues. Type VIII collagen was found in highly fibrillar arrays in the ocular sclera, in the meninges surrounding brain, spinal cord, and optic nerve, and in periosteum, perichondrium, meninges, and the subendothelial layer of blood vessels (Kapoor et al., 1988; Kittelberger et al., 1990; Sawada et al., 1990).

Kapoor et al. (1988) described the distribution of collagen type VIII in tissues from a single calf with immunofluorescence using an anti-type VIII collagen monoclonal antibody. There was linear staining of DM in the cornea, but no fluorescence in the stroma or Bowman's membrane. Despite elaborated attempts to «unmask» epitopes, collagen type VIII could not be demonstrated in aortic intima or media by immuno-fluorescence. Other tissues were also negative for type VIII collagen, concluding lens, kidney, lung, and liver. From these results it can be concluded that type VIII collagen is not a structural component of basement membranes, but that this unusual collagen is a component of certain specialized extracellular matrices, several of which are derived for the neural crest (Kapoor et al., 1988). In this study Kapoor did not find collagen type VIII in the bovine kidney.

Immunohistochemical studies by Rosenblum (1994) show that type VIII collagen is expressed diffusely in the glomerular subendothelium. Kittelberger et al. (1989) have identified type VIII collagen in sheep glomerular arterioles and the larger renal branch arterie but not in intraglomerular cells.

It is hypothesized by Rosenblum (1994) that type VIII collagen is expressed both as a polymer and as a monomer within the glomerulus, and may serve unique functions depending on its conformation (Rosenblum,

1994). In the stroma of the cornea collagen type VIII is expressed in its monomeric form in association with collagenous fibrils. There it may serve as a molecular bridge between different types of matrix molecules (Rosenblum, 1994).

The discovery of several types of molecules that appear to act as molecular bridges between different types of matrix components or as specialized scaffolds has enhanced the understanding of the three dimensional structure of ECM's in normal tissues. Fibrillar associated collagens with interrupted triple helices (FACIT), decorin, and the short-chain collagens are candidate «molecular bridge» molecules (Rosenblum et al., 1993). The possibility has been raised that «molecular bridge» molecules such as collagen type VIII may serve a similar function in the glomerulus (Rosenblum et al., 1993).

Function

Collagen type VIII has been found in several tissues. The function of collagen type VIII can be different in these tissues. The general function of type VIII collagen may be to provide porous, open structure than can withstand compressive force (Olsen and Ninomiya, 1993).

Recently, cDNA clones of one chain in VIII-3(α1[VIII]) were sequenced by Yamaguchi et al. (1989). Based on the length of the domains, they suggested the α1(VIII) was the backbone of the hexagonal lattice in the cornea, thereby stabilizing this membrane.

Iruela-Arispe et al. (1991) examined the expression of type VIII collagen as a function of angiogenesis *in vitro*. Their data show an upregulation of SPARC (Secreted Protein, Acidic and Rich in Cysteine) and collagen types I and VIII, in both microvascular and microvascular endothelial cells, actively forming vascular cords. Since type VIII collagen is significantly downregulated after cells reach confluence, even the modest increases detected by Western blotting are likely to be relevant to the phenomenon of angiogenesis. They speculate that collagen type VIII might facilitate the assembly of endothelial cords and tubes, and that this protein is associated with the developing mammalian and avian cardiovascular system, particularly in the myocardium and endocardiac cushions, as well as in embryonic capillaries and some large vessels.

Three functions of collagen type VIII are proposed. Collagen type VIII may play a role in angiogenesis (Iruela-Arispe et al., 1991), collagen type VIII may provide an open structure to stabilize several basement membranes (Yamaguchi et al., 1989), and it may polymerize and interact with matrix components to form extracellular matrix (Rosenblum et al., 1993).

Collagen type VIII in disease

Normal matrix components are overexpressed in chronically diseased mesangial matrix. Increased volume of the mesangium may be determined by enhanced

proteoglycan expression, observed early in the disease. This, in turn, may stimulate mesangial cells to produce fibrillar collagens resulting in a fibrillar noncompliant mesangial matrix (Rosenblum, 1994).

The mesangial matrix is probably regionally diverse with respect to the organization of its components. Thus, within specific areas of the mesangium different types of matrices serve a distinct function (Rosenblum, 1994). Rosenblum et al. (1990) recently described the presence of collagen type VIII in the glomerulus. This protein can be overexpressed during chronic glomerular diseases and may therefore play a role in the development of glomerulosclerosis (Rosenblum, 1994).

The high predicted pI of the noncollagenous NC1 and NC2 domains of α1-VIII collagen suggest that this collagen may interact with negatively-charged ECM and cell surface molecules such as proteoglycans (Rosenblum et al., 1993). The interaction of α1-VIII collagen with heparan sulphate might define a pore size which could limit the filtration of macromolecules from the glomerular capillary into the mesangium (Rosenblum, 1994) and may cause damage to kidney tissue.

C1q is a collagen-like subcomponent of the first complement component (Coremans, 1995). There is a significant sequence homology with the C-terminal domain of human collagen α1(X), the human α2[VIII], and the human C1qA, C1qB and C1qC complement chains. The area of homology is extended over approximately 130 residues (Sellar et al., 1991; Thomas et al., 1991).

Anti-C1q antibodies which recognize the collagen-like region of C1q, have crossreactive epitopes with collagen type II (Coremans, 1995). Anti-C1q antibodies can be shown in systemic and renal diseases like membrane-proliferative glomerulonephritis, glomerulosclerosis, systemic lupus erythematosus (SLE), anti-GBM nephritis (Siegert et al., 1992). SLE is a systemic disease mediated by auto antibodies. C1q plays a role in the development of renal injury in Graft-versus-Host disease induced in mice, a model for SLE (Coremans, 1995).

Since C1q also has a homology with collagen type VIII, the C1q antibody might cross-react with this type of collagen as well. This has not yet been investigated, but might be considered. If there is cross-reactivity, collagen type VIII may play a role in the development of renal injury through this interaction with anti-C1q antibodies.

How the changes in matrix composition alter the structure and function of the mesangial matrix, and the precise role of collagen type VIII in kidney diseases remains to be defined (Rosenblum, 1994).

Collagen type X

Structure

Type X collagen is a non-fibrillar component of the extracellular matrix of the hypertrophic zone of the growth plate cartilage (Reginato et al., 1995). The human α1(X) gene has been mapped to the q21-q22 region of chromosome 6 (Apte et al., 1991).

The type X molecule is comprised of three apparently identical polypeptides of Mr 59,000 known as α1(X) chains (Yamaguchi et al., 1989; Kwan et al., 1991). Polypeptide chains of collagen type X contain three distinct domains (Fig. 1): a short non-collagenous amino-terminal domain region of 52 amino acid residues, a collagenous domain of 460 amino acid residues, and a collagenous carboxyl-terminal domain of 162 amino acid residues (Yamaguchi et al., 1989). Ten amino acid residues upstream from the translational stopcodon, a hydrophobic segment is localized (Ninomiya et al., 1986). The amino acid sequence derived from the gene reveals several points mutations in the collagenous triplet structure. Five point mutations are of the type Gly-X-Gly and three point mutations are of the type Gly-X-Y-X-Y-Gly (Ninomiya et al., 1986).

The nonfibrillar nature of type X collagen has been clearly demonstrated by immunoelectron microscopy and this finding is consistent with gene cloning studies, which suggested that type X collagen belongs to a family of collagens distinct from the fibrillar collagen family (Kwan et al., 1991). Another difference between collagen type X and fibrillar collagen type is that collagen type X is produced by only one cell type.

Cellular source

Recently, it was discovered that hypertrophic chondrocytes, localized to presumptive mineralization zones of hyaline cartilage, produce type X collagen (Ninomiya et al., 1986). The extracellular matrix surrounding chondrocytes, mineralizes to be replaced by bone marrow and subsequently bone in the epiphyseal growth plate (Rooney et al., 1993). Hypertrophic chondrocytes elaborate the assembly of type X collagen into a matlike structure within the matrix (Kwan et al., 1991). This has led to the concept that type X collagen may be associated with the process of mineralization (Rooney et al., 1993). Rapid remodelling of extracellular matrix accompanies the changes from collagen type II to type X expression in newly formed hypertrophic chondrocytes, preceding both vascular invasion and calcification of the matrix (Iyama et al., 1994).

Growth plate chondrocytes produce several types of collagens, mostly type II and at least three other types, including IX, X, and XI. Type II collagen is a major component of cartilage and is produced by small, proliferating chondrocytes together with types IX and XI collagen (Lu Valle et al., 1989). As soon as the collagen type X gene is expressed the protein is detectable in the cytoplasm of hypertrophic chondrocytes and in the pericellular matrix (Sage and Iruela-Arispe, 1990). As soon as chondrocytes transform from the proliferating to the hypertrophic type, collagen type II expression decreases. The collagen type X gene starts to be

expressed in these transitional cells at the same time (Iyama et al., 1994).

Tissue distribution

Type X collagen is not a component of most cartilaginous tissues since it is not synthesized by actively growing chondrocytes (Ninomiya et al., 1986). Only in the matrix of the hypertrophic zone of the epiphyseal growth plate cartilage can type X collagen be found (Gibson and Flint, 1985; Kielty et al., 1985; Kwan et al., 1986a,b; Ninomiya et al., 1986). The only data is support of a type X collagen network *in vivo* is provided by Schmid and Linsenmayer (1990) who observed an irregular filamentous network of type X collagen in ultrathin sections of embryonic chick cartilage. Claassen and Kirsch (1994) studied the distribution of type X collagen in thyroid cartilages of various ages. Their results show that type X collagen is first detected in thyroid cartilage of 18- to 21-year-old adults. Studies of tissue distribution of collagen type X revealed that it is absent in resting and rapidly growing cartilage and in bone, therefore type X collagen represents a transient and developmentally regulated collagen (Ninomiya et al., 1986). Synthesis of the collagen type X molecule has also been demonstrated in the cartilaginous callus formed during bone repair (Grant et al., 1987).

Function

Despite the detailed studies on the immuno-localization and characterization of collagen X (Kwan et al., 1986a,b; Ninomiya et al., 1986; Grant et al., 1987; Chu et al., 1988) the exact functional role of type X collagen in the cartilage has remained undefined (Farquharson et al., 1995; Olsen, 1995; Reginato et al., 1995), in part because there is no clear information regarding the ultrastructural organization of this molecule and the interactions of collagen type X with other components in the extracellular matrix (Kwan et al., 1991). However the sites of the synthesis of collagen type X and the timing of its appearance in the growth plate have led investigators to postulate that collagen X is involved in the process of endochondral ossification (Kwan et al., 1989).

Kwan et al. (1991) and Sawada (1982) found that type X collagen produces a hexagonal structure within the cartilage extracellular matrix. Formation of this hexagonal structure will alter the existing properties of the matrix and this alteration can make the hypertrophic region angiogenic, triggering endothelial cell proliferation, type VIII collagen synthesis and cell migration (Rooney et al., 1993). Type X collagen in hypertrophic cartilage can provide a scaffold to prevent local collapse as the cartilage matrix is removed during endochondral ossification (Kirsch and von der Mark, 1990; Olsen, 1995). It is possible that collagen type X may be involved in angiogenesis rather than in mineralization (Rooney et al., 1993).

Collagen type X in disease

To date, there is increasing evidence that heritable diseases affecting endochondral bone formation, such as chondrodysplasias, and other diseases of cartilage such as osteoarthritis may be associated with abnormalities in the structure or expression of type X collagen (Reginato et al., 1995). For example, autosomal dominant metaphyseal chondrodysplasia type Schmid (MCDS) is characterised by metaphyseal abnormalities, combined with dwarfism. The collagen type X gene was an obvious candidate gene based upon the tissue specific expression of COL10A1, and MCDS was indeed found to be associated with mutations in this gene (Olsen, 1995).

Warman et al. (1993) analyzed genomic DNA from individuals with osteochondrodysplasias to determine whether endochondral ossification in humans affected by abnormalities in the type X collagen gene. They found a 13 bp deletion in one family with MDCS. The normal type X collagen which can be synthesized is reduced since the deletion prevents association of the mutant polypeptide during trimmer formation (Warman et al., 1993).

Examination of patients with MDCS reveal a paucity of trabecular bone in the metaphysis and a compressed zone of hypertrophic chondrocytes (Warman et al., 1993).

McIntosh et al. (1994), Dharmavaram et al. (1994) and Bonaventure et al. (1995) also showed that mutations in the COL10A1 locus cause cartilage disorders. Rosati et al. (1994) studied long bone development in type X collagen null mice and found no bone abnormalities. They suggest that bone growth and development can only be modified by the presence of abnormal type X collagen, and that the function of type X collagen may be fulfilled by other ECM proteins in its absence (Rosati et al., 1994).

Functional relationship between collagen types VIII and X

Collagen types VIII and X show several similarities in structure and perhaps in function. Iruela-Arispe et al. (1991) suggested that the collagen types VIII and X both play a role in the process of angiogenesis. Ingber and Folkman (1988) have shown that metabolic reduction of collagen synthesis inhibits capillary formation on the chicken chorioallontoic membrane (CAM), suggesting that collagen might be a necessary substratum for the migration of endothelial cells. Rooney et al. (1993) have investigated whether induced angiogenesis *in vitro* and *in vivo*, is associated with collagen synthesis. This study implied that both collagen types VIII and X may play a role in the process of angiogenesis by modifying the extracellular matrix and stimulating cell migration. Rooney et al. (1993) also reported that angiogenesis *in vivo* is associated with the deposition of collagen fibrils on the CAM and with specific, increased production of

type I and type VIII collagens by bovine aortic endothelial cells (BAEC) (Rooney et al., 1993). Thus, in essence, the precise role of collagens in angiogenesis is still unclear.

A difference between type VIII and X collagen is that collagen type X distribution is restricted to hypertrophic cartilage, whereas type VIII is distributed in various tissues including DM, vascular subendothelial matrices, heart, liver, kidney, lung, and perichondrium, as well as several malignant tumors including Ewing's sarcoma, astrocytoma, and hepatocellular carcinoma (Kittelberger et al., 1990; Sage and Iruela-Arispe, 1990).

Although much is known about the structures of the short-chain collagen types, further studies will have to be performed in order to obtain more detailed information about the function of collagen type VIII and X.

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